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Investigation of Poly(amidoamine) Dendrimer Based Simvastatin Oral Formulations: Pharmacokinetic and Pharmacodynamic Studies

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Abstract
Dendrimers have a highly branched nanoscale architecture with low polydispersity and high functionality. Therefore, dendrimers been widely used for nanocarriers in drug delivery systems. This paper gives an overview of the recent progress on the evaluation of pharmacokinetic and pharmacodynamic (PK/PD) profiles of PAMAM dendrimers based Simvastatin (SMV) oral formulation in rats. The mechanism of the dendrimer delivery of SMV will be also presented.

Keywords: dendrimer, statin, drug delivery, PAMAM

Statin is known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor and is used to treat patients with hypercholesterolemia. Simvastatin (SMV) is a member in the statin class of pharmaceuticals; it is cost-effective and has relatively few adverse effects. Thus, SMV becomes the best choice in initial therapy for hypercholesterolemia. However, SMV is severely limited by its poor aqueous solubility and low oral bioavailability through the gastrointestinal track. Such drawbacks could be gentled by a drug delivery system, which can efficiently deliver SMV and improve pharmacokinetics of SMV. Dendrimers have been extensively utilized for construction of nanocarriers in drug delivery systems. Dendrimers have a highly branched nanoscale-architecture with low polydispersity and high functionality. This unique architecture allows for high drug payload and multifunctionality [1-3]. PEGylated PAMAM dendrimer was reported to possess high biocompatibility, enhanced solubility and slow release of SMV in vitro comparing to the non-PEGylated dendrimer [4], as shown in Figure 1. It was of interest to evaluate the in vivo potential of PEGylated dendrimer-SMV formulation.

For the first time, Kulhari et. al. evaluated the pharmacokinetic and pharmacodynamic (PK/PD) profiles of PAMAM dendrimers based SMV oral formulation in rats. This formulation was formed by complex of dendrimers and SMV as follows. Noncovalent electrostatic interactions initiated SMV attachments onto the dendrimer surface groups. The hydrophobic interiors of dendrimers provided a lipophilic environment where SMV could be entrapped. This simple encapsulation of SMV significantly enhanced aqueous solubility of SMV, which could lead to a sufficient increase in SMV oral bioavailability. Surface groups of dendrimers played an important role in this formulation. PEGylated dendrimers exhibited a higher SMV encapsulation efficiency than amine and hydroxyl dendrimers. This phenomenon could be explained by that PEG chains on the dendrimer surface provided large void space and entanglement potential for SMV encapsulation. As a result, PK profiles displayed that 7.5-fold increase in total amount of SMV absorption and 3.8-fold decrease in elimination rate of SMV were achieved in the case of rats treated with PEGylated dendrimer-SMV comparing to free SMV. These PK profiles suggested that PEGylated dendrimer-SMV complexes increased SMV solubility, slowly released SMV, prolonged SMV exposure time, reduced SMV elimination rate, and subsequently, enhanced SMV bioavailability. PD profiles exhibited that 1.8-fold decrease in serum cholesterol level, 2.2-fold decrease in LDL

cholesterol level, and 3.7-fold increase in serum HDL cholesterol level were achieved in the case

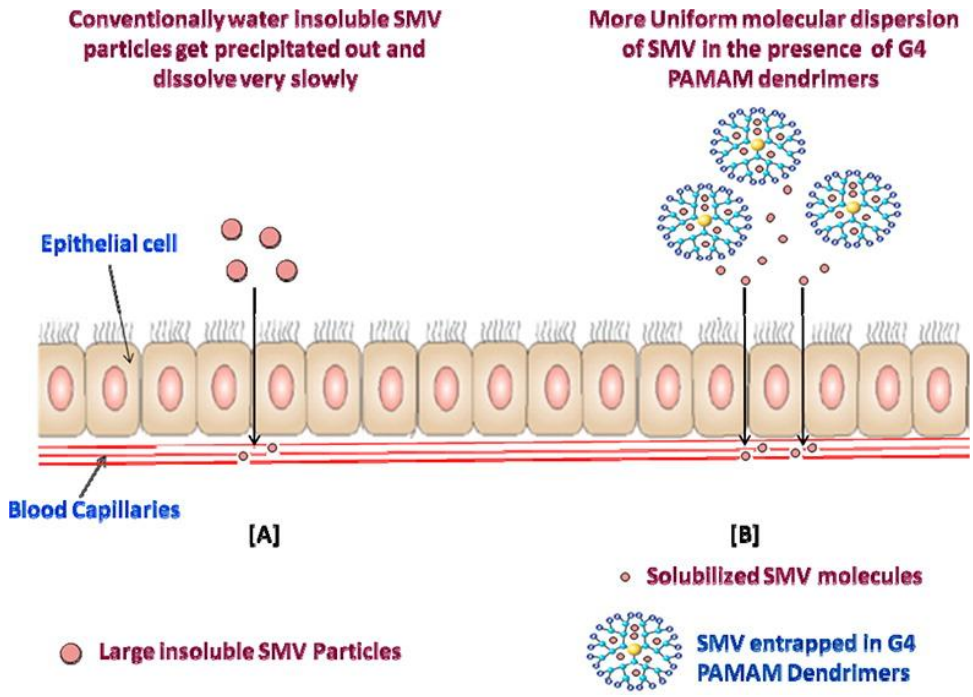

Figure 1. Mechanism of dendrimer delivery of SMV. (Reproduced from reference [5]. Copyright 2013 Clearance Center, Inc.)

of rats treated with PEGylated dendrimer-SMV comparing to free SMV. These PD profiles suggested that the slow release kinetics of SMV from PEGylated dendrimer-SMV complexes sustained a steady-state SMV concentration in the blood. All these results well align with in vitro release kinetics of SMV from this formulation [5].

In summary, Kulhari et. al. have clearly illustrated the PEGylated dendrimer-SMV formulation can improve PK/PD profiles of SMV, and it can tender the decrease in total required drug amount, in dosing frequency, and hence, in potential toxicities of SMV. Kulhari et. al. provided a platform to enhance bioavailability and reduce adverse effects in the effort of successful SMV oral delivery.

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